REMARKS

Claims 1-19 are pending in this application. All of the claims stand rejected under 35 U.S.C. § 112, first paragraph, as purportedly not enabled. This rejection and other issues raised in the Office Action of November 6, 2002 will be addressed below.

The specification has been amended to comply with the requirements for applications containing nucleotide and/or amino acid sequences. The marked up version of the specification is attached hereto and is captioned "Version with Markings to Show Changes Made to the Specification."

I. Compliance with Sequence Listing Requirements.

The Office Action states that the present application fails to comply with the requirements for applications containing nucleotide and/or amino acid sequences as set forth in 37 C.F.R. § 1.821 through 1.825. The Office Action further indicates that it was accompanied by a Notice to Comply with Requirements for Patent Applications Containing Nucleotide and/or Amino Acid Sequence Disclosures which specified the deficiencies in the present application.

Applicant notes that the present Office Action was not accompanied by the indicated Notice to Comply. The Applicant has reviewed the specification and found one amino acid sequence on page 13. Accordingly, an amendment is submitted herein to amend page 13 to add the proper sequence identifier. In addition, paper and computer-readable copies of the sequence listing are enclosed herewith. This is a bona fide attempt to comply with the regulations regarding applications containing amino acid and/or nucleotide sequences. If there are additional sequences in the application that the Applicant has inadvertently overlooked, it is respectfully requested that a Notice to Comply be issued indicating the nature of the alleged defects in the application.

II. Enablement.

Claims 1-19 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement, the Examiner stating that the specification does not describe the claimed

subject matter in such a way as to enable one skilled in the art to make and/or use the invention. This rejection is respectfully traversed below.

A. Legal Standards of Enablement.

The "test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." (MPEP §2164.01, citing *In re Wands*, 858 F.2d 731, 737). With respect to the present application, the Examiner has provided no objective evidence to doubt the veracity of Applicant's specification, or that the invention does not work as described. The Patent Office has the affirmative burden to set forth such evidence in order to establish even a *prima facie* case of non-enablement (MPEP § 2164.04; *In re Wright*, 999 F.2d 1557 (Fed. Cir. 1993); *In re Marzocchi*, 439 F.2d 220, 224 (CCPA 1971)). Thus, the rejection should be withdrawn.

The Office Action expresses concern that Applicant has not demonstrated actual reduction to practice of particular embodiments of the invention. The Applicant notes that disclosure in the specification of an actual reduction to practice is *not* necessary to satisfy the enablement requirement (*see*, MPEP §2164.02; *Gould v. Quigg*, 822 F.2d 1074, 1078; 3 USPQ 2d 1302, 1304 (Fed. Cir. 1987)).

Assuming, *arguendo*, that there are some embodiments of the invention in which administration of a compound to a subject does not result in inhibition of EMAP II activity, the Applicant respectfully notes that MPEP §2164.08(b) provides that the existence of inoperative embodiments within the scope of a claim does not necessarily render a claim non-enabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with the expenditure of no more effort than is normally required in the art.

Moreover, the Court of Appeals for the Federal Circuit has held that it is not necessary for the specification or claims to list all operative embodiments, or to exclude all inoperative embodiments, stating: "Even if some of the claimed combinations [are] inoperative, the claims are not necessarily invalid. 'It is not a

function of the claims to specifically exclude ... possible inoperative substances...' ". *Atlas Powder Co. v. DuPont*, 750 F.2d 1569; 224 USPQ 409 (CAFC 1984). All that is required by § 112 is that one skilled in the art may determine the inoperative embodiments with no more than routine skill. The Applicant submits that this standard is satisfied in the present application.

As discussed in more detail below, the present specification (Example 1) describes improved myocardial function in an animal model of myocardial infarction by inhibiting the anti-angiogenic activity of EMAP II by administration of an antibody against EMAP II. In view of this discovery, the present claims are enabled as one skilled in the art could follow the teachings in the specification and the knowledge in the art to carry out other embodiments of the invention. *See In re Strahilevitz*, 668 F2d 1229; 212 USPQ 561 (CCPA 1982).

In view of the foregoing discussion, Applicants respectfully submit that the subject matter of the pending claims is enabled, and respectfully request that the outstanding rejection on this basis be withdrawn.

B. **Claims 1-19 are Enabled.**

Claims 1-19 stand rejected under 35 U.S.C. § 112, first paragraph on the basis that "[t]here is a high level of unpredictability in the art for any method of treatment with a therapeutic agent for treating a disease...." (Office Action, page 3, third paragraph). The Applicant submits that this rejection does not satisfy the legal standards for maintaining an enablement rejection, as set forth above. The Applicant has, in fact, demonstrated improved myocardial function by administering an anti-EMAP II monoclonal antibody in an animal model of myocardial infarction (discussed in more detail below). Accordingly, the Applicant submits that one skilled in the art would be able to carry out other methods of inhibiting EMAP II activity to achieve the claimed effects without undue experimentation. Accordingly, the Applicant submits that the present rejection under § 112, first paragraph should be withdrawn.

The Office Action specifically discusses methods reciting antibodies and methods reciting antisense oligonucleotides. These two concerns will be addressed separately below.

(i). **Antibodies.**

Claims 3 and 13 specifically recite methods comprising administering "an antibody that specifically binds to EMAP II" in an amount "effective to stimulate vascular growth in [said] cardiac muscle" (Claim 3) or in an amount "effective to promote blood vessel formation in [said] cardiac muscle" (Claim 13).

The Office Action states, in part:

> Furthermore, although the antibody art is more established, and antibodies to EMAPII are known in the art (see IDS reference 1, for instance), one skilled in the art would necessarily practice undue experimentation to use such antibodies, or to make and use other antibodies to EMAPII for the claimed functions in any whole organism, facilitating vascular growth in cardiac muscle. Neither the specification nor the art teach a nexus for administration of any EMAPII antibody to whole organisms for the claimed functions. Specifically, the factors considered unpredictable are (1) dosage, (2) site of action, (3) route of administration, and (4) toxicity, such that one skilled in the art would be able to make and use the invention as claimed. If the necessary site of action for EMAPII is inside the cardiac muscle cell, it is unpredictable that an antibody would be able to enter the cell to act on the target protein. Similarly, one skilled in the art would necessarily practice "trial and error experimentation" to use any antibody to EMAPII in any whole organisms for the methods of treatment claimed.

(Office Action, paragraph spanning pages 5-6).

The Applicant respectfully disagrees with this rejection. First, Applicant notes that the present specification does, in fact, demonstrate effectiveness of the claimed methods *in vivo*. In Example 1, describes administration of a rabbit EMAP II antibody by intraperitoneal injection post-infarction in rats that had been subjected to ligation of the left anterior descending artery. Additional doses were administered every third day for a total of three treatments. Several indicia of myocardial function were evaluated at various time-points (data presented in Table 1). As reported in Example 1, statistically significant improvements were observed for cardiac output, stroke volume and shortening fraction. Inhibition of the anti-angiogenic effects of EMAP II with the anti-EMAP II antibody improved diastolic function and ventricular contractility.

Accordingly, there is no objective basis for rejecting Claims 3 and 13 for lack of enablement. The Office Action indicates that factors such as dosage, route of administration, and toxicity, and the like render the presently claimed invention of Claims 3 and 13 unpredictable. The Applicant disagrees. Now that Applicant has demonstrated inhibition of EMAP II by administration of an anti-EMAP II antibody by an intraperitoneal route, one skilled in the art may readily identify other effective antibodies, routes of administration, and dosages without undue experimentation using routine methods known in the art and the present specification and working examples as a guide. Further, although toxicity is not dispositive of the enablement inquiry (*e.g.*, a method of administering a therapeutic compound, such as a chemotherapy agent, may produce substantial toxicity in the subject but nonetheless be enabled and quite valuable to the medical community), in view of the Applicant's disclosure, one skilled in the art may optimize the dosages, routes of administration, and the like to reduce any toxic effects as a result of administration of the compound.

Further, the state of the art indicates that antibodies are well-recognized as effective therapeutic agents. The Applicant submits herewith a number of abstracts from the PubMed database, which illustrate the state of the art with respect to antibody therapies. Hortobagyi, (2001) *Semin. Oncol.* **28**:43, is an exemplary publication describing the effectiveness of trastuzumab ("herceptin"), a monoclonal antibody that has been found to be effective in treatment of breast cancers over-

expressing HER2/neu. Use of monoclonal antibodies as therapeutic agents has been reported in patients with non-Hodgkin's lymphoma (anti-CD20 MAb, anti-CD52w MAb, anti-class II HLA MAb, anti-CD22 MAb; Tsai et al., (2000) *Clin. Lymphoma* 1:62; Press et al., (2001) *Am. Soc. Hematol. Educ Program* 1:221), rat renal allograft recipients (anti-CD28 MAb; Laskawski et al., (2002) *J. Am. Soc. Nephrol.* 13:519), patients with Wegener's granulomatosis (anti-CD20 MAb; Specks et al. (2001) *Arthritis Rheum.* 44:2836), experimental autoimmune glomerulonephritis in rats (anti-CD8 MAb; Reynolds et al., (2002) *J. Am. Soc. Nephrol.* 13:359), and a patient with Kaposi sarcoma-associated herpesvirus-related multicentric Castleman disease (anti-CD20 MAb; Carbellino et al., (2001) *Blood* 98:3473). Trophy et al., (2001) *Curr. Opin. Pharmacol.* 1:265, describes the use of monoclonal antibodies for the treatment of pulmonary disease. Moreover, this publication notes that seven monoclonal antibodies have received regulatory approval from the FDA since 1997 and concludes that "monoclonal antibody therapy has come of age."

In sum, in view of the guidance provided in Applicant's specification, the working examples, and the acceptance in the art of the therapeutic efficacy of antibody therapies, the Applicant submits that Claims 3 and 13 are enabled. Accordingly, the Applicant requests that the outstanding enablement rejection be withdrawn.

(ii). <u>Antisense oligonucleotides</u>.

Claims 5 and 15 specifically recite methods of administering an antisense oligonucleotide. The Office Action states that these methods are not enabled on the basis that antisense therapies are unpredictable. This rejection is respectfully traversed below.

The Office Action states that "[o]ne of skill in the art would not accept on its face the successful delivery of any antisense molecule to EMAPII...." (Office Action, page 4, third paragraph). The Applicant submits that the enablement inquiry does not require that every possible antisense oligonucleotide to EMAP II elicit the claimed effect. The existence of inoperative embodiments is not dispositive. The issue is whether it would require undue experimentation to identify antisense oligonucleotides

having the claimed effects. Methods of producing and delivering antisense molecules are well known in the art. The Office Action points out many of the known factors to be considered in designing an antisense oligonucleotide. In view of Applicant's demonstration that inhibition of EMAP II protein post-infarction in an animal model can improve myocardial function (Example 1), one skilled in the art would be able to routinely identify an antisense oligonucleotide to the EMAP II sequence having similar effects.

The Office Action suggests that antisense technology has not been successfully employed in the treatment of any disease state. Toward this end, the Applicant includes herewith a copy of a publication by Galderisi et al., (1999) *J. Cellular Physiology* **181**:251, and an abstract by Orr, (2001) *Curr. Opin. Mol. Ther.* 3:288, which report the use of antisense oligonucleotides as selective inhibitors of gene expression as well as the first antisense-based drug. It was found that the antisense oligonucleotide Fomiversen was effective in the treatment of cytomegalovirus retinitis in patients with AIDS. Phase III trials have been completed on this drug, and it has received market approval. Therefore, antisense technology has been successfully employed in the treatment of a disease state.

In view of the foregoing, the Applicant respectfully submits that one skilled in the art could practice the invention of Claims 5 and 15 without undue experimentation. Accordingly, Applicants request that the outstanding enablement rejection be withdrawn.

III. Conclusion.

The points and concerns raised by the Examiner in outstanding Office Action having been addressed in full, it is respectfully submitted that this application is in condition for allowance, which action is respectfully requested.

Respectfully submitted,

Karen Magri

Karen A. Magri
Registration No. 41,965

Enclosures: Galderisi et al.
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CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Box Sequence, Commissioner For Patents, Washington, DC 20231, on February 6, 2002.

Sloan Hobbs
Date of Signature: February 6, 2002

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Version with Markings to Show Changes Made to the Specification

Page 13, lines 7-12:

Synthesis of antibody. The antibody is generated from the following peptide sequence:

(C)DAFPGEPDKELNP (#252-264) (SEQ ID No: 1)

(C) is a cysteine that is assigned for use in the single point, site-directed conjugation procedure described below, and is not part of the original EMAP II antibody.

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